

Pharmacology of Abused Drugs : Principles, Cannabis, Opiates, Cocaine, and Amphetamines

Michael J. Bohn, M.D.

Clinical Associate Professor

University of Wisconsin Medical School

Today's Topics

- **General Principles**
- **Pharmacokinetics:** How drugs enter, move in, and leave the body
 - Absorption, Distribution, Metabolism
- **Pharmacodynamics:** How drugs affect the body (therapeutic & toxic effects)
 - Brain/neural effects: therapeutic, intoxication, addictive [reinforcers of drug-taking and other behavior, tolerance, withdrawal]
 - Other organ effects
- **Drug Classes:** Cannabinoids, Opiates, Cocaine, Amphetamines
- **Next Time:** Nicotine, Barbiturates, Benzodiazepines, Hallucinogens, PCP/Ketamine

Drug Pharmacokinetics: Absorption

- **MAJOR DETERMINANTS: ROUTE & DRUG's CHEMICAL AND PHYSICAL PROPERTIES**
- **EFFECTS:**
 - **PERCENT OF DOSE THAT ENTERS BODY,**
 - **RATE OF RISE OF BLOOD (TISSUE LEVELS)**

Drug Absorption: Administration Routes

- **ORAL:** Pills, liquids (opiates, amphet, etc), solids (halluc)
- **TRANSDERMAL:** Skin Patches (nicotine, clonidine)
- **TRANSMUCOSAL:** Oral (smokeless tobacco, oral cocaine)
Nasal (cocaine, amphetamines)
- **PULMONARY:** (inhalants, nicotine, crack, ice/meth, MJ)
- **INTRADERMAL:** Skin popping (opiates)
- **INTRAMUSCULAR:** (opiates, some benzos)
- **INTRAVENOUS:** (cocaine, amphet, heroin, other opiates)

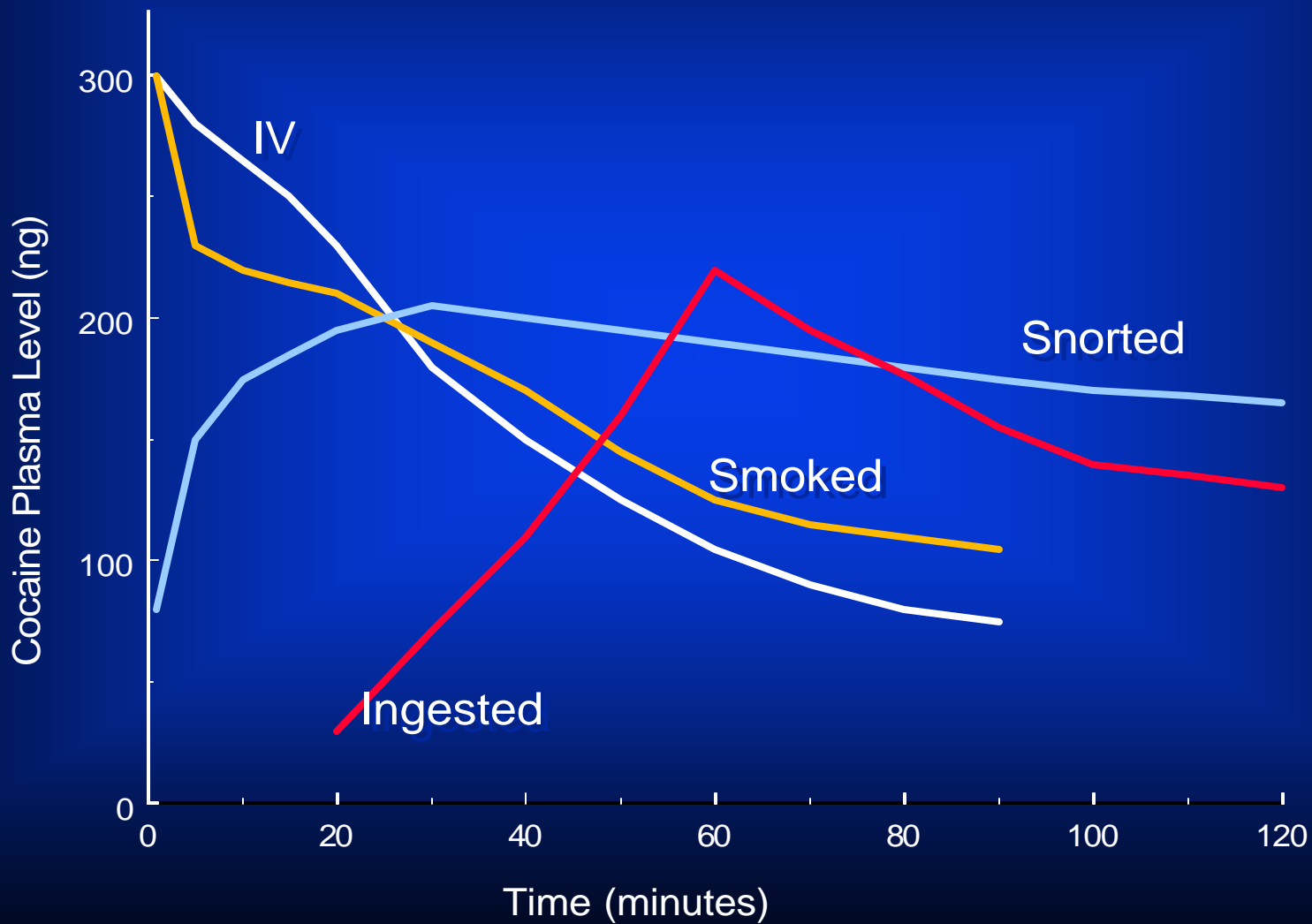
Drug Absorption: Oral Route

- **Drug passes into acid environment of stomach, which can inactivate drug and reduce absorption→low blood levels**
 - **Example:** oral cocaine
- **Binders can slow release from pill, slowing rate of rise in blood levels**
 - **Examples:** Oxycontin vs. oxycodone, Ritalin SR vs. Ritalin
- **Fat solubility→ more rapid absorption**
 - **Example:** Diazepam vs. clonazepam
- **Disease and surgery to gut can remove or damage absorptive region→lower absorption**
- **Blood draining gut enters liver, where first pass metabolism occurs→ lowered blood levels**

Transdermal, Transmucosal, and Pulmonary Drug Absorption

- Avoid first pass effect as blood not drained into liver → higher blood and tissue levels
- Absorption increased by absorptive surface area (lung >> skin)
- Absorption increased by large blood supply (nicotine-dilates vessels, cocaine-constricts)

Cocaine Plasma Levels



From Hatsukami and Fischman, 1996

Drug Pharmacokinetics: Distribution

- **MAJOR TISSUE DETERMINANTS: BLOOD FLOW, FAT CONTENT, SPECIFIC BINDING SITES FOR DRUG AND ITS METABOLITES**
- **MAJOR DRUG DETERMINANTS:**
 - **FAT SOLUBILITY OF DRUG (THC)**
 - **BINDING OF DRUG TO RECEPTOR TYPES**

Drug Metabolism

- **MOSTLY IN LIVER, BUT ALSO IN BLOOD AND OTHER TISSUES**
- **CAN LEAD TO ACTIVATION, INACTIVATION, REMOVAL**
 - **ACTIVATION:** codeine→morphine, heroin→morphine
 - **CONVERSION TO ACTIVE METABOLITE:** cocaine→benzoylecognine, diazepam→desmethyldiazepam
 - **REMOVAL:** hepatic (liver) oxidation and conjugation, then excretion in bile, to feces, or via kidneys for most drugs
- **HALF-LIFE IS KEY MEASURE**

PHARMACODYNAMICS: HOW DRUGS ACT ON CELLS & ORGANS

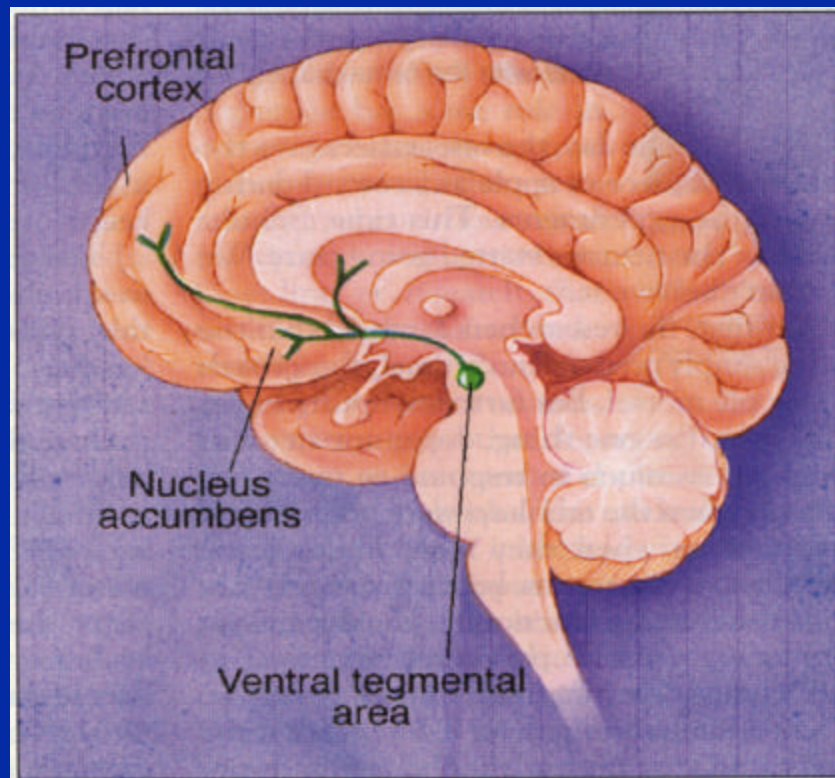
- **BINDING:** TO VERY AVID, SPECIFIC RECEPTOR MOLECULES, USUALLY ON CELL SURFACE, WITH SLOW DISSOCIATION FROM RECEPTOR
 - ANTAGONISTS BIND MORE AVIDLY TO RECEPTORS, SATURATING THEM AND PREVENTING NEW DRUG FROM BINDING (naloxone, naltrexone)
- **ACTIVATION OF INTRA-CELLULAR RESPONSE**
 - ACTIVATE NORMAL SECOND MESSENGERS e.g., cGMP
 - THIS LEADS TO ENZYME ACTIVATION TO CHANGE STRUCTURE AND ACTIVITY OF KEY REGULATORY PROTEINS IN CELLS and CAN ALTER CELL MEMBRANES QUICKLY (e.g, altering firing rates)
 - THIS MAY ALTER GENE EXPRESSION FOR ONE OR A BATTERY OF GENES, LEADING TO LONG-LIVED CELL CHANGES (e.g., synapses that encode memories)

PHARMACODYNAMICS: HOW DRUGS ACT ON CELLS & ORGANS

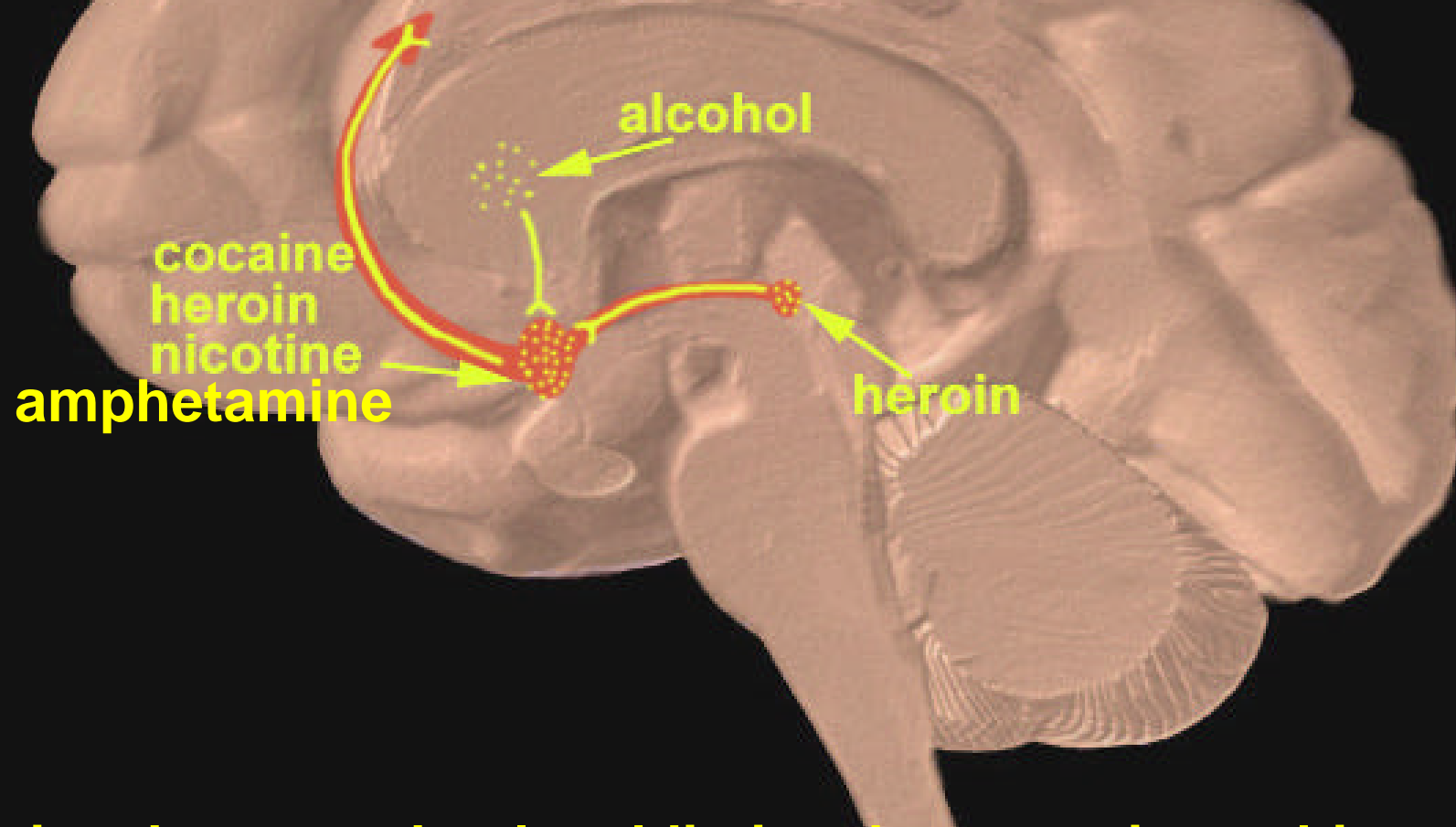
- **USE PATHWAYS SIMILAR OR IDENTICAL TO THOSE USED BY MANY NORMAL HORMONES & NEUROTRANSMITTERS**
- **MANY DRUG RECEPTORS HAVE NORMAL BINDING COMPOUNDS ISOLATABLE FROM NORMAL BRAINS, SO POTENTIAL FOR THERAPEUTIC EFFECT**
 - Opiate receptors: enkephalins, endorphins
 - THC receptors: prostaglandin-like compounds

“Reward” Pathways in the brain

The mesocorticolimbic dopamine pathway



Activation of the reward pathway by addictive drugs



addictive drugs, and only addictive drugs, activate this pathway

Addictive Substances Markedly Increase Dopamine (DA) Release

Reward

Peak DA Release

FOOD, SEX:

50-100%-

ETHANOL

125-200% -

CANNABIS [THC]

125-175%

NICOTINE

225%-

MORPHINE/HEROIN

150-300% -

COCAINE

400% -

AMPHETAMINE

1000% -

RA Wise, 2000

Heroin and Other Opiates

> 20 active opiate compounds in use

Two classes: natural, poppy-based (morphine, heroin) and synthetic (codeine, methadone, fentanyl)

Complex 3-dimensional multi-ring structure for these alkaloids

Many therapeutic uses, including treatment of pain, heart failure, and cough (dextromethorphan)

Typical routes are oral and IV, but some is smoked (opium), injected SQ (heroin skin popping), and snorted (heroin)

Opiate Pharmacokinetics

Fairly good oral absorption for most opiates (exceptions are meperidine (Demerol) and morphine)

Distributed to brain, spinal cord, cardiac and lung tissue

Rapid distribution and short half life predicts high abuse potential

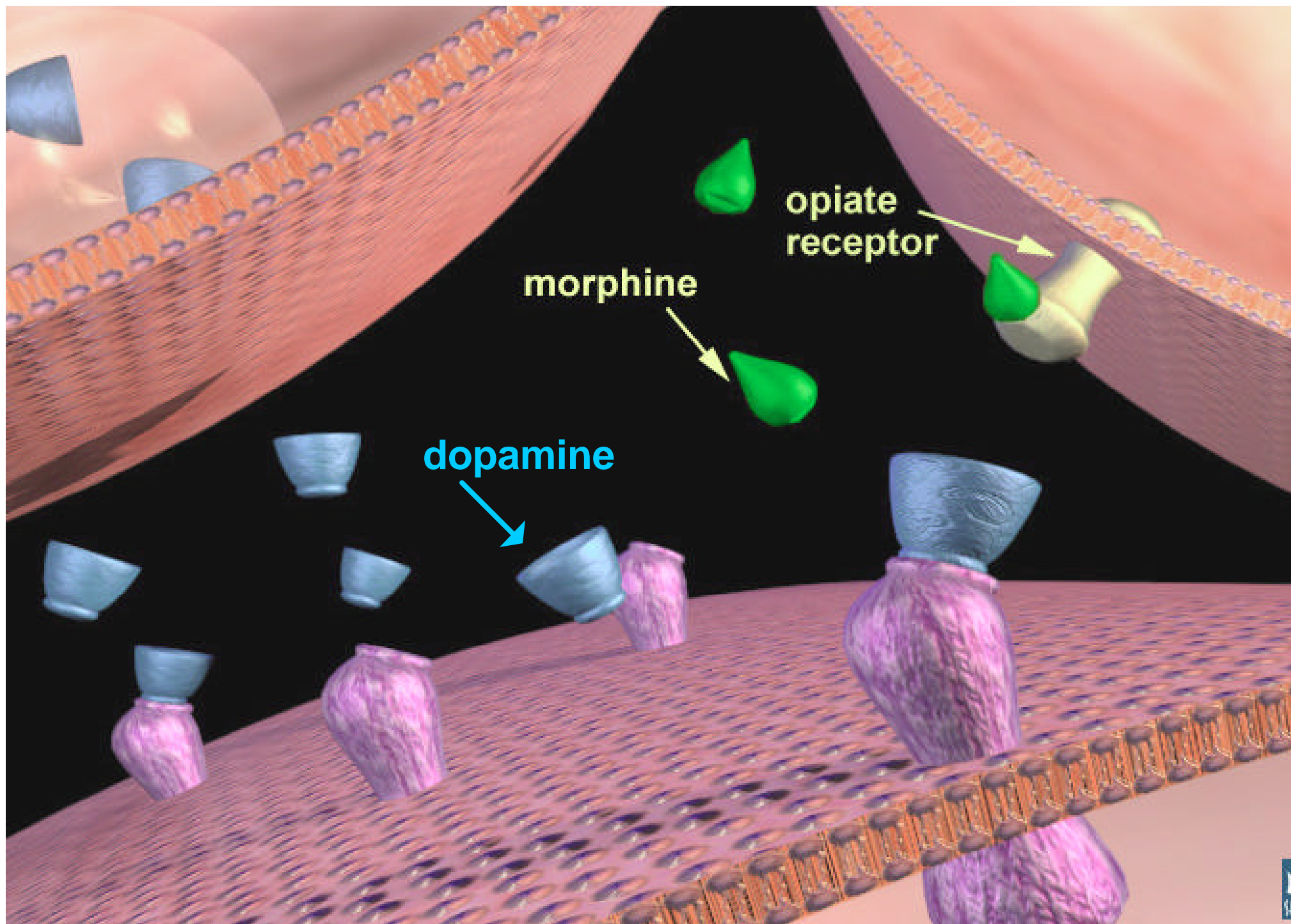
Half lives vary widely from few hours to 12-24 hours

Some require activation to form active compounds:
codeine → morphine, heroin → morphine

Others yield toxic compounds if given repeatedly:
meperidine → normeperidine → seizures

Opiate Receptors: Types and Binding Agents

- 3 major types of opiate receptors: mu, delta, & kappa, all couples to G proteins that regulate GTP levels
- All these types of receptors have genes that have been cloned
- Each has agonists (drug-like effects) and antagonists
- Endogenous peptides bind to specific opiate receptor type (enkephalin-delta, endorphin-mu, dynorphin-kappa)
- Other opiate receptors are orphan and endomorphin receptors, each with its own endogenous agonists



Mu, Delta, and Kappa Receptors: ***Locations & Effects***

<u>Region</u>	<u>major agonist effect</u>
spinal cord	analgesia
medulla	anti-emesis, inhibit respiratory drive
VTA	reinforcement, inhibit GABA→DA release
cerebellum	incoordination
eye	miosis (fine pupil)
gut	reduced acid secretion, slow motility
VTA	reinforcement
gut	decreased peristalsis→constipation
VTA	dysphoria

Opiate tolerance & withdrawal

Can develop after single dose, but usually after prolonged use

Onset, duration related to mu receptor dissociation rate

Unclear if protracted abstinence occurs and is separate from depression

Tolerance has several molecular mechanisms: receptor phosphorylation (PKC), compensatory increase cAMP path/AC activity due to CREB, & decrease G proteins

Withdrawal due to excess cAMP and increased excitatory glutamate in LC → increased NE output; increased GABA and increased glutamate in VTA → less DA → dysphoria

Opiates: Use Freq. & Withdrawal Course

Drug	Usual freq. of use (hr)	Appearance of wdwl sx's (hrs)	Peak (hrs)
meperidine	2-3	4-6	8-12
hydromorphone	3	4-5	
heroin	4	8-12	48-72
morphine	5-6	14-20	
codeine	3	24	
methadone	8-24	36-72	72-96

Typical Duration of Withdrawal

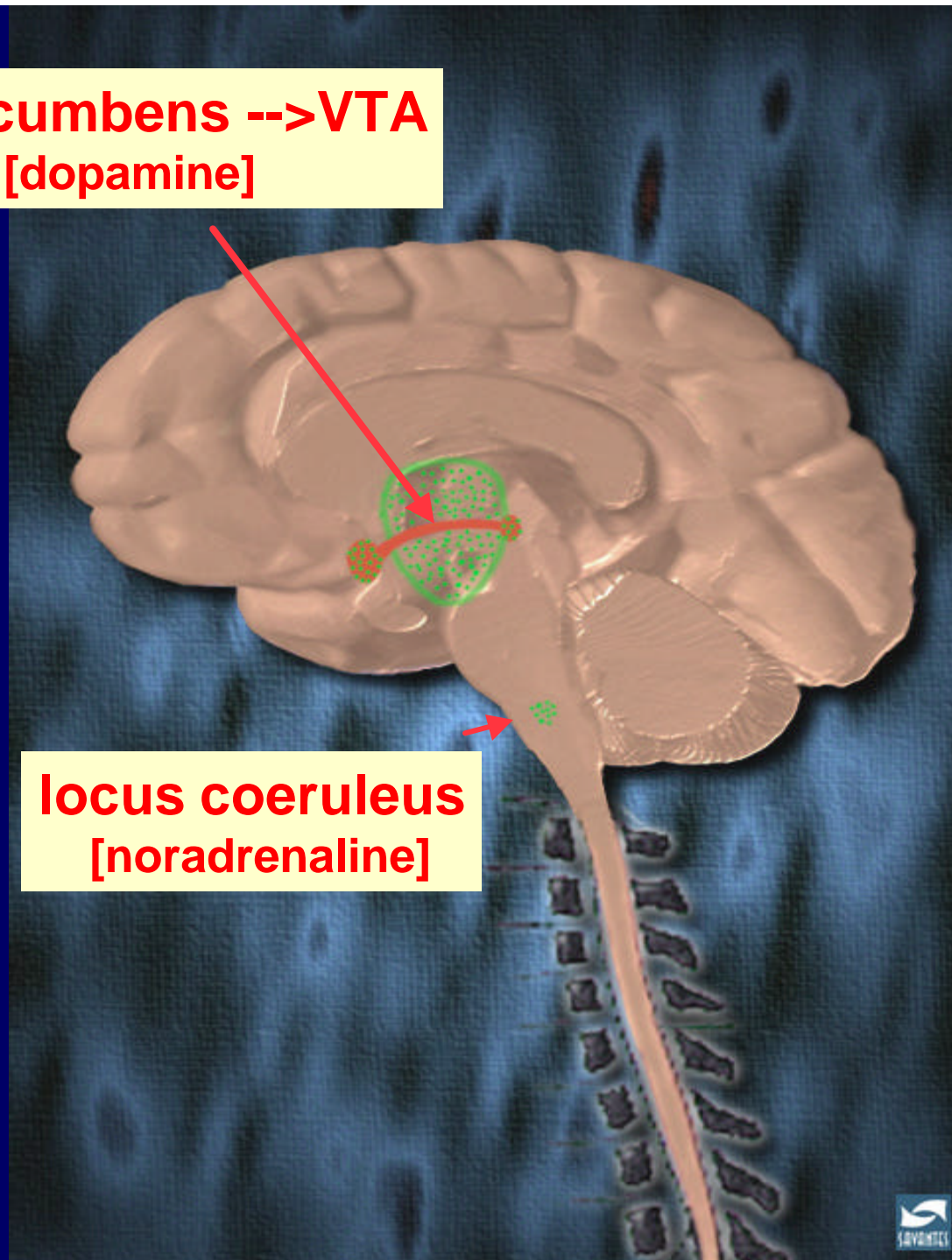
heroin	5-10 days
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Methadone	14-21 days
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adapted from Kleber, 1994

N. accumbens --> VTA
[dopamine]

locus coeruleus
[noradrenaline]



From Bozarth and Wise (1985) "Toxicity associated with long-term intravenous heroin and cocaine self-administration in the rat"

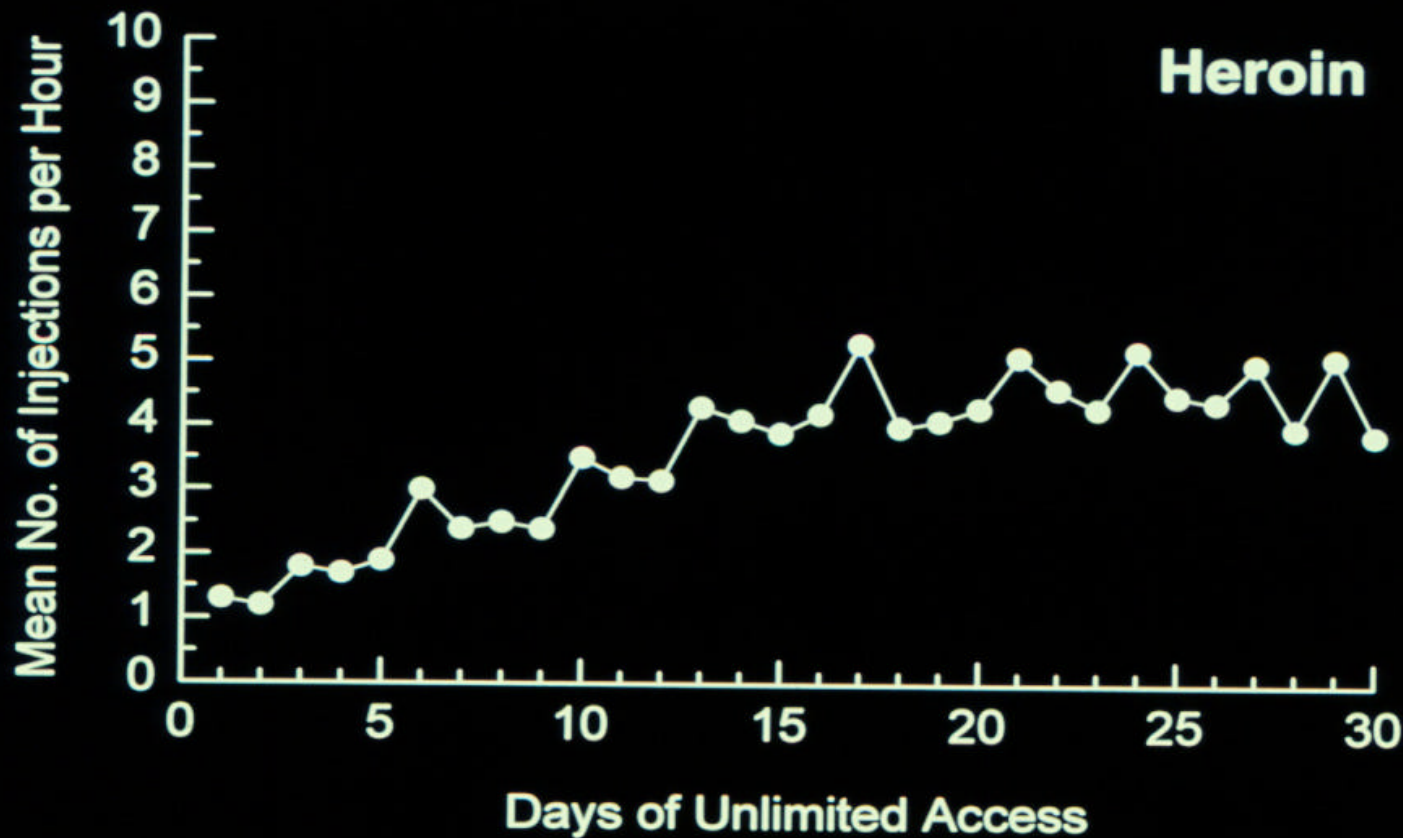


Fig 1. Daily intake of drug for typical subject self-administering heroin hydrochloride, 100 $\mu\text{g/kg}$ per infusion